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| 09/056,343 | 04/07/98 | LOEVBORG U | 3556.224-US |

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| **ART UNIT** | **PAPER NUMBER** |
| 1652 | 12 |

**DATE MAILED:** 08/22/00

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/056,343 | LOEVBORG, UFFE | |
| | Examiner | Art Unit | |
| | William W. Moore | 1652 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

**Status**

1)☒ Responsive to communication(s) filed on *16 June 2000*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *24-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____.

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

**Attachment(s)**

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
18) ☐ Interview Summary (PTO-413) Paper No(s). _____.
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

## DETAILED ACTION

### *Continued Prosecution Application*

The request filed on June 16, 1999, Paper No. 11, for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/056,343 is acceptable and a CPA has been established. An action on the CPA follows.

### *Specification*

As noted in Paper No. 10 mailed December 16, 1999, this application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is still required. In responding to the restriction requirement stated in Paper No. 6 mailed January 21, 1999, Applicants elected species A for prosecution in Paper No. 7 filed February 9, 1999, a method of producing industrial and process enzymes described in claims 25-29, as well as variant products of claims 33-34. The restriction requirement was rescinded and claims 24-34 were examined on the merits in Paper No. 8 mailed April 26, 1999. No amendment or argument accompanied Paper No. 9 filed October 22, 1999, responsive to the rejections and objections of record, and Paper No. 10 restated the indications of informalities and the rejections of record first stated in Paper No. 8. Paper No. 11 presents no amendments or arguments addressing the rejections of record which are again restated herein.

### *Requirement of a Terminal Disclaimer*

The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78(d). Effective January 1, 1994, a

registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 24-28 and 32-34 remain rejected for reasons of record under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-18 of U.S. Patent No. 5,766,898. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 24-28 and 32-34 herein have a scope which embraces the subject matters of claims 1-18 of the issued patent.

*Claim Rejections - 35 USC §112*

Claims 24-29 and 32-34 remain rejected for reasons of record under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for a method practiced with a polypeptide **having a known amino acid sequence**, and for a variant product of a native peptide having a known amino acid sequence wherein a native epitope is identified and altered, does not reasonably provide enablement for methods practiced with a polypeptide the amino acid sequence of which is unknown or for a variant product of a polypeptide the native amino acid sequence of which is unknown. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

A determination that distinct epitopes, distinguishable from other epitopes, reside on the surface of a native polypeptide requires no knowledge of the structure(s) that form an individual epitope because a monoclonal antibody raised to the purified, polypeptide may detect one among them, yet the claimed method requires that an epitope be altered, and this cannot be practiced blindly. Claims 30, 31 and 35-39 are unaffected by the rejection of record because the amino acid sequences of the great majority of the proteins used in the practice of medicine have been determined and all isocoding DNA sequences specifying any of these proteins may be generated with a computer program. Where an amino acid sequence of a medicinal protein is yet to be determined, it will have been isolated for its use in medicine, permitting ready amino acid sequence determination.

No method of changing the amino acid composition of surface and internal features or a protein that form an individual epitope is practicable unless the primary structure of the polypeptide - its amino acid sequence - has first been determined. The claimed methods include the prediction of an epitope, and all methods for predicting epitopes practiced in

the prior art made of record herewith require a determination of a polypeptide's amino acid sequence. Nothing in the process steps of claim 24, from which claims 25-29 and 32-34 depend, links its "immunological and proteochemical methods" of identifying an epitope to a recited "mutation of a DNA molecule encoding for the expression of said parent protein". The degree of experimentation required to randomly prepare, *de novo*, altered epitopes in yet-to-be-isolated polypeptides through solid-phase peptide synthesis is deemed to be undue because any successful attempt to alter a native epitope requires that knowledge of the amino acid sequence of the polypeptide. The mere availability of a monoclonal antibody provides no indication of the area or length of a native epitope, its amino acid composition and the order of amino acids therein, or whether other features beyond the primary structure of the polypeptide in the region of the epitope contributes to its presence and immunogenicity.

It is well settled that 35 U.S.C. §112, first paragraph, requires that a disclosure be sufficiently enabling to allow one of skill in the art to practice the invention as claimed without undue experimentation and that unpredictability in an attempt to practice a claimed invention is a significant factor supporting a rejection under 35 U.S.C. §112, first paragraph, for non-enablement. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (recognizing and applying "*Forman*" factors). Cf., *Ex parte Forman*, 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986) (citing eight factors relevant to enablement). The standard set by the CCPA, the predecessor tribunal of the Court of Appeals for the Federal Circuit, is not to "make and screen" any and all possible alterations because a reasonable correlation must exist between the scope of guidance provided by the specification and the scope asserted in the claimed subject matter. *In re Fisher*, 427 F. 2d 833, 839, 166 USPQ 18, 25 (CCPA 1970) (scope of enablement varies inversely with the degree of unpredictability of factors involved in physiological activity of small peptide

hormone). See also, *Ex parte Maizel*, 27 USPQ2d 1662, 1665 (Bd. Pat. App. & Int. 1992) (functional equivalency of divergent gene products not supported by disclosure only of a single B-cell growth factor allele). There is no isolation step or amino acid sequence determination step in the claimed process and given, 1) the lack of any guidance in the specification and in prior art for determining the composition and size of an epitope without first determining the amino acid sequence of the polypeptide, 2) the absence of any working examples wherein an epitope of a polypeptide is altered without knowledge of its amino acid sequence, 3) the absence of support in the state of the art and level of skill in the art for such alteration as evidenced by the publications of record herein, and 4) the unpredictability in the art that, until the present day, requires foreknowledge of the amino acid sequence of polypeptide in order to define and alter an epitope, the scope of the claimed subject matter embraced by claims 24-29 and 32-34 is not supported by the present specification. One way to overcome this rejection would be to limit the subject matter of claim 24 as indicated in the statement at page 3, lines 10-13, hereinabove.

The following is a quotation of the second paragraph of 35 U.S.C. §112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 24, 25, 30 and 39 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Line 5 of claim 24 is inaccurate in indicating that a "DNA molecule cod[es] for the expression of a protein". A DNA sequence which is a coding region cannot, by itself, promote its transcription and the subsequent translation of its transcript as a polypeptide. Additional DNA is required to mediate the expression of a polypeptide in a particular cell. Even though ancillary regulatory nucleotide sequence that flank a polypeptide-encoding region may promote transcription and guide translation in some cells, they will not be able to do so in other cells and a coding DNA sequence cannot

influence cellular transcription. Since the claim provides for a vector at line 7 that will maintain a DNA segment encoding either or both of the parent protein and the variant protein, the concept of expression need not be ambiguously mixed with the capacity of a DNA sequence to encode a polypeptide. At line 8, claim 24 recites "wherein said vector is functional" but does not indicate the functions the vector possesses, rendering the claim vague and indefinite. Claim 24 also recites at line 8 "wherein . . . or whereby" but fails to indicate which are the agents of, or subjects for, these terms. Are they the same - e.g., the vector of unspecified function - or do they differ? No corrective language is apparent for suggestion to overcome this aspect of the rejection and Applicant must determine what the intended subject matter should be and how to clearly describe it.

Claims 25 and 30 are indefinite in reciting "said protein" in referring back to claim 24, which discusses two polypeptides, an unmodified epitope-bearing parent protein and a modified variant protein. This aspect of the rejection may be overcome by amending both claims to recite instead "the parent protein". Claim 39 is indefinite in reciting "which is another protein" where there is no specific, reference, protein described in claim 32 from which claim 39 depends. Amending claim 39 to delete "which is another protein" will overcome this aspect of the rejection.

*Claim Rejections - 35 USC §§102 and 103*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 24 and 32 remain rejected for reasons of record under 35 U.S.C. §102(b) as being clearly anticipated by Luo et al., 1988, **Virology**, Vol. 163, pages 341-348, of record.

Luo et al. disclose the mapping of protein epitopes with an immunological method, monoclonal antibody recognition, and a "proteochemical" method, protease digestions, and their application to subsequent determinations of the epitopes, and then discloses the how to identify in recombinantly synthesized DNA molecules the nucleotide changes that will produce amino acid changes resulting in, p. 343 and Table 1 at page 344, "at least 60-75% reduction in antigenicity" in three different protein variants.

Claims 24 and 32 remain rejected for reasons of record under 35 U.S.C. §102(b) as being clearly anticipated by Keil et al., 1989, **Virology**, Vol. 170, pages 392-407, of record.

Keil et al. disclose the mapping of protein epitopes with an immunological method, monoclonal antibody recognition, informed by a proteochemical analysis, protease foot-printing, and subsequent determination of the sites of several epitopes in the protein, as well as the preparation by recombinant DNA synthesis of nucleotide changes in DNA molecules encoding the protein resulting in deletions that produce internally truncated variants of the protein. Keil et al. disclose that these deletions resulted in, see Figure 7 and variant products designated vWK3, vWK13 and vWK16, a complete loss of some epitopes and a reduction in antigenicity of others.

Claims 24 and 32 remain rejected for reasons of record under 35 U.S.C. §102(b) as being clearly anticipated by Choo et al., 1988, **Human Immunology**, Vol. 21, pages 209-219, of record.

Choo et al. disclose identification of a protein epitope by an immunological method, monoclonal antibody recognition, and a proteochemical analysis, isoelectric focussing gel electrophoresis, in order to subsequently determine the site of the epitope in the protein and the preparation of recombinant DNA molecules encoding either the native protein or a variant protein wherein the variant had reduced antigenicity due to a nucleotide change in the DNA sequence resulting in, p. 213, "only a single amino acid difference at position 59" in one of the four domains of the protein "when compared to the prototype", or native, protein.

Claims 25-27, 30, 31, 33-35 and 39 remain rejected for reasons of record under 35 U.S.C. §103(a) as being unpatentable over any one of Choo et al., Keil et al., or Luo et al., as applied to claims 24 and 32 above, in view of Baxter et al., U.S. Patent No. 5,258,287, Greenfield et al., U.S. Patent No. 4,894,443, Hopp et al., 1981, **Proceedings of the National Academy of Sciences, U.S.A.**, Vol. 78, pages 3824-3828, Zachariae et al., 1981, **Allergy**, Vol. 36, pages 513-516, and Favre et al., 1989, **Molecular Immunology**, Vol. 26, pages 17-25, all of record.

The disclosures of Choo et al., Keil et al., or Luo et al., discussed hereinabove, are taken as before. Discussing alteration of the amino acid sequence of a medically-significant human polypeptide which binds the peptide hormone, insulin-like growth factor, Baxter et al., available as prior art under 35 U.S.C. §102(e), teach at lines 1-66 of col. 7, that "[s]ubstantial changes in . . . immunological identity are made by selecting [amino acid] substitutions [introduced as codon substitutions in the underlying DNA sequence] that are less conservative than those in Table 1", and, while "[m]ost deletions and insertions, and substitutions in particular are not expected to produce radical changes in the characteristics of the [native] polypeptide molecule", any uncertainty about "the exact effect of the [chosen] substitution, deletion or insertion . . . when modifying . . . an immune epitope . . . will be evaluated by routine screening assays". Baxter et al. specifically teaches, id. at lines 61-64, that "a change in the immunological character of the [native polypeptide], such as affinity for a given antibody, is measured by a competitive-type immunoassay".

While Baxter et al. are concerned with a polypeptide not an enzyme, Greenfield et al., also available as prior art under 35 U.S.C. §102(e), teach at cols. 7-8 that native epitopes present in the microbial- or plant-derived enzyme portion of an antibody-enzyme conjugate may identified and "remove[d] . . . by partial proteolytic digestion or by chemical modification" as well as "by cloning and expressing the gene encoding its amino acid sequence" wherein "the epitopes [in the product of genetic engineering] may be removed at the DNA level by recombinant DNA techniques".

Hopp et al. generally teach a series of factors useful in the computer analysis of amino acid sequences in order to predict the antigenic determinants - epitopes - of proteins when provided only the knowledge of their amino acid sequence. Hopp et al. teach, Table 4, their predictions of the primary epitopes in 18 prominent polypeptides of immunogenic significance, including three human interferons. Hopp et al. teach their conclusion, page 3827, of results of an experiment in which the immunogenicity of the first epitope indicated in Table 4 was altered by chemical synthesis of a peptide region comprising the hexapeptide wherein the side chains, residues, of amino acids flanking the hexapeptide were chemically altered to shield their hydrophilic nature, bringing about a failure of antibodies specific for the native peptide region to bind it. Favre et al. teach that a polypeptide, gamma-interferon, used in medical therapy can present epitopes which give rise to antibodies limiting its effectiveness, and map several such epitopes with monoclonal antibodies. Zachariae et al. teach that producing a microbial protease purified from a *Bacillus* species - an enzyme having a known amino acid sequence and wide industrial applications such as formulation of detergents - presents health problems for persons exposed to it because their immune systems became sensitized to the purified protease, whereby further exposures produce allergic reactions in a significant number of such persons.

In view of the successes in identifying and altering the immunogenicity of specific epitopes in polypeptides disclosed by Choo et al., Keil et al., or Luo et al, as well as the teachings of Baxter et al. and Greenfield et al. of general approaches for reducing the immunogenicity of medically significant polypeptides and enzymes, it would have been obvious to one of ordinary skill in the art at the time the invention was made to apply the teachings of Hopp et al. and of Favre et al. of identification of interferon epitopes by means, respectively, of computer analysis of amino acid sequences and monoclonal antibody mapping, to identify epitopes in the amino acid sequence of a medicinal protein such as a gamma-interferon, and to then alter those sequences, by altering the underlying DNA sequence according to teachings of Baxter et al. and Greenfield et al., to abolish or diminish the immunogenicity of those epitopes. This is because Favre et al. teach that epitopes present on interferons may limit their medicinal use, because Hopp et al. teach how to identify the antigenic epitopes in a given interferon, native amino acid sequence, and because Baxter et al. and Greenfield et al. teach how to alter or reduce the immunogenicity of epitopes, once identified, by non-conservatively altering the known amino acid sequence of an enzyme or of a medically significant polypeptide by altering the codons of the DNA sequence that encodes it.

It would also have been obvious to one of ordinary skill in the art in view of the teaching of Zachariae et al. of an industrial enzyme, a protease which presents a health problem to persons handling it, to identify epitopes in the amino acid sequence of an industrial protease utilizing the teachings of Hopp et al. and to then alter the amino acid sequences by altering the underlying DNA sequence according to teachings of Baxter et al. and Greenfield et al., to abolish or diminish the immunogenicity of those epitopes. This is because Zachariae et al. point out the need to solve the problem of immunogenicity of the native protease, because Hopp et al. teach how to identify the antigenic epitopes in a

given, native amino acid sequence, because Baxter et al. and Greenfield et al. teach how to alter or reduce the immunogenicity of epitopes in proteins, once identified, by non-conservatively altering the known amino acid sequence of an enzyme by altering the codons of the DNA sequence that encodes it, and because of the successes in identifying and altering the immunogenicity of specific epitopes in polypeptides disclosed by any of Choo et al., Keil et al., or Luo et al.

Claim 36 remains rejected for reasons of record under 35 U.S.C. §103(a) as being unpatentable over any one of Choo et al., Keil et al., or Luo et al. in view of Baxter et al.('287), Greenfield et al.('443), and Hopp et al., as applied to claims 24, 32 and 35 above, and further in view of Ruttenberg, U. S. Patent 3,903,068, of record.

The disclosures of Choo et al., Keil et al., or Luo et al., discussed hereinabove, are taken as before, as are the further teachings of Baxter et al., Greenfield et al., and Hopp et al. Ruttenberg generally teaches that chemical and enzymatic treatment of porcine insulin will convert its amino acid sequence which presents an epitope immunogenic in humans into the amino acid sequence of human insulin, abolishing its immunogenicity. In view of the successes of any among Choo et al., Keil et al., or Luo et al, in identifying and altering the immunogenicity of specific epitopes in polypeptides, as well as the teachings of Baxter et al. and Greenfield et al. of general approaches for reducing the immunogenicity of polypeptides and enzymes and the further teaching of Hopp et al. of identifying epitopes when the amino acid sequence of the polypeptide is known, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use recombinant DNA technology as taught by Baxter et al. and Greenfield et al. to change the amino acid sequence of an insulin produced by one mammalian species to the amino acid sequence of an insulin of a mammalian species in which its medicinal use is desired, such as human insulin, to remove an epitope that can raise an unwanted immune response in the desired species, as Ruttenberg had laboriously done, since recombinant expression of a genetically altered, immunogenic epitope-free, insulin would clearly be economically advantageous.

Claims 37 and 38 remain rejected for reasons of record under 35 U.S.C. §103(a) as being unpatentable over any one of Choo et al., Keil et al., or Luo et al. in view of Baxter et al.('287), Greenfield et al.('443), and Hopp et al., as applied to claims 24, 30, 32 and 35 above, and further in view of Fulton et al., U. S. Patent No. 4,970,300, of record.

The disclosures of Choo et al., Keil et al., or Luo et al., discussed hereinabove, are taken as before, as are the further teachings of Baxter et al., Greenfield et al., and Hopp et al. Fulton et al. generally teach that chemical treatment of purified human Factor VIII permits the conjugation thereto of non-antigenic polymers in order to reduce, col. 2 at lines 48-56, the production of inhibitory antibodies raised by infusion of human Factor

VIII to treat clotting disorders in as many as 14% of patients receiving such treatment. Fulton et al. also teach, col. 2 at lines 3-7, that the Factor VIII gene had been cloned permitting recombinant production of human Factor VIII. In view of the successes of any among Choo et al., Keil et al., or Luo et al, in identifying and altering the immunogenicity of specific epitopes in polypeptides, as well as the teachings of Baxter et al. and Greenfield et al. of general approaches for reducing the immunogenicity of polypeptides and enzymes and the further teaching of Hopp et al. of identifying epitopes when the amino acid sequence of the polypeptide is known, it would have been obvious to one of ordinary skill in the art at the time the invention was made to determine the amino acid sequence of Factor VIII from the cloned gene and scan that amino acid sequence with the computer analysis taught by Hopp et al. in order to identify the potential epitopes that contribute to the formation of anti-Factor VIII antibodies in as many as 14% of the patients who receive it in infusions to treat clotting disorders in order to apply the teaching of Baxter et al. of recombinant DNA technology in changing the amino acid sequence of each potential epitope in turn to reduce the immunogenicity of native Factor VIII in its desired medicinal use as a clotting enzyme.

Claims 28, 29 and 34 remain rejected reasons of record under 35 U.S.C. §103(a) as being unpatentable over any one of Choo et al., Keil et al., or Luo et al. in view of Baxter et al.('287), Greenfield et al.('443), Hopp et al. and Zachariae et al. as applied to claims 24, 25, 32 and 33 above, and further in view of Nielsen et al., U. S. Patent No. 4,560,651, of record.

The disclosures of Choo et al., Keil et al., or Luo et al., discussed hereinabove, are taken as before, as are the further teachings of Baxter et al., Greenfield et al., and Hopp et al. Nielsen et al. generally teach the purification of an amylase from a *Bacillus* species in order to use it in processes for treating starches to convert them to syrups and also teach, cols. 5-6, that the amylase is likely to be sufficiently immunogenic in mammals to generate antibodies in them that will recognize its particular epitopes and allow industrial process

users of the amylase to distinguish it from amylases produced by other strains of the same *Bacillus* species as well as to distinguish it from other microbial amylases. In view of the teaching of Zachariae et al. that an enzyme purified from a microbial source, a *Bacillus* species, for further applications in industrial can present a health problem to persons handling it by sensitizing their immune systems, and also in view of the successes of any of Choo et al., Keil et al., or Luo et al, in identifying and altering the immunogenicity of specific epitopes in polypeptides, it would have been obvious to one of ordinary skill in the art at the time the invention was made to determine the amino acid sequence of the amylase by standard procedures in the art and to utilize the teachings of Hopp et al. to identify epitopes in its amino acid sequence and to then alter the amino acid sequences by altering any isocoding DNA sequence that may be synthesized to specify that amino acid sequence according to teachings of Baxter et al. and Greenfield et al., to abolish or diminish the immunogenicity of those epitopes. This is because such an artisan at that time could reasonably expect that enzymes originally produced by microbes can be immunogens for persons regularly exposed to them and that the amylase purified by Nielsen et al. would be placed in commercial production for use in starch processing, thus exposing persons to it in purified form, and could be made less immunogenic. This is because such an artisan at that time could reasonably expect that determining the amino acid sequence of the amylase would permit identification of its potential epitopes by the method of Hopp et al. and that suitable changes in the amino acid sequence would be produced by application of the teachings of Baxter et al. and Greenfield et al., to abolish or diminish the immunogenicity of those epitopes by changing the appropriate codons in a synthetic gene designed to specify the native amylase amino acid sequence.

*Conclusion*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is (703) 308-0583. The examiner can be reached Monday through Friday from 9:00 AM to 5:30PM

EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. Papers related to this application may be submitted to Group 1800 by facsimile transmission. The faxing of such papers must conform with the notice published November 15, 1989 in the Official Gazette, 1096 OG 30. Informal and unofficial communications may be sent to the Art Unit 1652 FAX number, (703) 308-0294. Official filings should be sent to the Technical Center 1600 FAX number which is (703) 308-4556.

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. §122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark Office on February 25, 1997 at 1195 OG 89. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

William W. Moore
August 21, 2000